Guidance for Industry

INDs for Phase 2 and Phase 3 Studies

Chemistry, Manufacturing, and Controls Information

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
May 2003
CMC

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides recommendations to sponsors of investigational new drug applications (INDs) on the chemistry, manufacturing, and controls (CMC) information that would be submitted for phase 2 and phase 3 studies conducted under INDs.[2] This document applies to human drugs (as defined in the Federal Food, Drug, and Cosmetic Act). The guidance does not apply to botanical drug products,[3] protein drug products derived from natural sources or produced by the use of biotechnology, or other biologics. The goals of the guidance are to (1) ensure that sufficient data will be submitted to the Agency to assess the safety, as well as the quality of the proposed clinical studies from the CMC perspective, (2) expedite the entry of new drug products into the marketplace by clarifying the type, extent, and reporting of CMC information for phase 2 and phase 3 studies, and (3) facilitate drug discovery and development.

The amount and depth of CMC information that would be submitted to the Agency depends, in large part, on the phase of the investigation, the testing proposed in humans, and whether the information is safety related. This guidance identifies CMC information that would be presented in information amendments (i.e., CMC safety information) and annual reports (i.e., corroborating information).

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[1] This guidance has been prepared by IND Reform Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMCCC) in the Center for Drug Evaluation and Research (CDER) at the FDA.

[2] Recommendations are provided in other guidances for CMC issues relating to pre-IND, end-of-phase 2 (EOP2), and pre-new drug application (NDA) meetings (e.g., guidance for industry on *IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Information*), and pre-new drug application (NDA) rolling submissions (guidance for industry on *Fast Track Drug Development Programs – Designation, Development, and Application Review*).

[3] Information on INDs for botanical drug products will be provided in FDA's forthcoming guidance for industry on *Botanical Drug Products* (draft published August 2000; 65 FR 49247).

The recommendations in this guidance are intended to provide regulatory relief for IND sponsors by providing greater flexibility in the collecting and reporting of data and by avoiding redundant submissions. Four areas of regulatory relief are as follows:

- Certain information that traditionally has been submitted in information amendments would be identified as corroborating information (see section II.B.2) and can be submitted in an annual report.
- The limited phase 2 corroborating information recommended in section III need not be submitted before initiation of phase 2 studies and can be generated during phase 2 drug development.
- The phase 3 corroborating information recommended in section IV need not be submitted before the initiation of phase 3 studies and can be generated during phase 3 drug development.
- The corroborating information and a summary of CMC safety information submitted during a subject-reporting period would be included in the annual report. Therefore, there should be no need for *general CMC updates* at the end of phase 1 or phase 2.

Although applicable to INDs that are sponsored by both commercial establishments and individual investigators, the guidance's greater value and relevance will be for commercial INDs.

For phase 1 submissions, sponsors can refer to the guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (phase 1 guidance).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Current Requirements

Under current regulations in the United States, use of a human drug product not previously authorized for marketing in the United States requires the submission of an IND to the Agency. FDA's regulations at 21 CFR 312.22 and 312.23, respectively, contain the general principles underlying the IND submission and the general requirements for content and format. Section 312.23(a)(7)(i) requires that an IND for each phase of investigation include sufficient CMC information to ensure the proper identity, strength or potency, quality, and purity of the drug substance and drug product. The type of information submitted will depend on the phase of the investigation, the extent of the human study, the duration of the investigation, the nature and source of the drug substance, and the drug product dosage form.

As clinical development of the drug product proceeds, sponsors can discuss with the Agency the type of CMC information that would be submitted to support the use of the drug in all investigational phases. The Agency encourages sponsors to meet with the CMC review team, if appropriate, before the initiation of or during phase 3 clinical trials to discuss issues and protocols that might affect the approvability of the NDA. The Agency will grant CMC-specific meetings when justified (see CDER's guidance on *IND Meetings for Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Information*).

B. General Principles

This guidance provides recommendations on CMC safety information and the limited corroborating information that should be submitted to support phase 2 and phase 3 studies. The scope of the guidance covers many different types of drug substances and drug products. Therefore, every recommendation may not be applicable to a particular drug substance or drug product. CMC safety information and corroborating information should be submitted in information amendments (21 CFR 312.31) and annual reports (21 CFR 312.33), respectively.

Under § 312.33 annual reports must be submitted during the ongoing development of the drug. With respect to CMC information, each annual report to the IND should include a summary of CMC safety information submitted in information amendments during the past year (i.e., subject-reporting period) and, when applicable, corroborating information. The annual report should also include updates of corroborating information or corrections to information previously provided to the IND that cannot be considered significant enough to warrant an information amendment.

FDA recommends that the sponsor carefully document its drug development program. This more-detailed information is often used to establish correlations between data generated during IND studies and the to-be-marketed product and to support other aspects of the NDA (e.g., process controls, justification of specifications) even when the submission of this information was not warranted during the IND studies.

1. CMC Safety Information

CMC safety information should be submitted to support the safe use of the drug. FDA reviews the safety information to determine whether a clinical hold on the IND is warranted. A summary of CMC safety information submitted during a subject-reporting period should be included in the annual report.

CMC safety information, as recommended in this guidance, and any other CMC information available to the sponsor that relates to the safe use of drug should be submitted in information amendments as follows:

- The CMC safety information identified in section III (Phase 2 Studies) should be submitted before initiation of the phase 2 studies. This information can be submitted during phase 1 or before the initiation of phase 2 studies.

- The CMC safety information identified in section IV (Phase 3 Studies) should be submitted before initiation of the phase 3 studies. This information can be submitted during phase 1 or phase 2 or before the initiation of phase 3 studies.

- When new information becomes available that relates to the safe use of the drug or when there are changes in previously submitted CMC safety information, the information should be submitted during IND clinical trials in an information amendment as the information becomes available.

FDA recommends that the sponsor carefully assess any changes in the drug substance and drug product manufacturing process or drug product formulation at any phase of clinical development to determine if the changes can directly or indirectly affect the safety of the product. For changes with a significant potential to affect the safety of the product (see examples below), an information amendment should be submitted that describes the changes and contains relevant information at a level of detail sufficient for an adequate review and assessment. When appropriate, this information should include data from tests on the drug substance and/or drug product produced from the previous manufacturing process and the changed manufacturing process to evaluate product equivalency, quality, and safety. In addition, when analytical data from tests on the drug substance and/or drug product demonstrate that the materials manufactured before and after are not comparable, sponsors should perform additional qualification and/or bridging studies to support the safety and bioavailability of the material to be used in the proposed trials and, when applicable, to support the quality of the trials.

The CMC safety concerns identified in the phase 1 guidance are equally applicable to phase 2 and phase 3.

CMC modifications throughout the IND process that can affect safety include, but are not limited to, a change in:

- the synthetic pathway used to manufacture the drug substance
  -- material change in one of the bond forming steps
  -- change in a solvent used for the last reaction and/or crystallization step
  -- change resulting in a different impurity profile
- the manufacturing process that can affect the quality of a drug substance produced by fermentation or derived from a natural source (plant, animal, or human)
- the manufacturing process that can directly or indirectly affect viral or impurity clearance for a drug substance produced by fermentation or derived from a natural source
- the manufacturing method from one manufacturing method (chemical synthesis, fermentation, or derivation from a natural source) to another
- source material (e.g., plant to animal, species, part used) or country of origin for a drug substance derived from a natural source
- species and/or strain of microorganism for a drug substance produced by fermentation
- certain aspects of specifications (see sections III.A.4, III.B.4, IV.A.4, and IV.B.4)

- the method of sterilization of the drug substance or drug product
- the route of administration
- the composition and/or dosage form of the drug product
- the drug product manufacturing process that can affect product quality
- the drug product container closure system that can affect product quality (e.g., metering capability, dose delivery)

2. Corroborating Information

Corroborating information is used to assess the scientific quality of the drug substance and drug product used in the clinical investigations to ensure that the clinical investigations will yield reliable and interpretable data and to corroborate the quality and safety of clinical materials used in earlier investigational phases.[4] Corroborating information is less likely to affect the safe use of the drug but should be submitted to ensure the proper identity, strength or potency, quality, and purity of the investigational drug (21 CFR 312.23(a)(7)(i)).

Corroborating information should be submitted in annual reports. In general, the corroborating information should focus on summaries and analyses of data rather than extensive compilations of data. However, there are some exceptions when compilations of data should be submitted (e.g., stability data). Occasionally, CDER may request more detailed corroborating information when warranted to assess the scientific quality of the investigations.

Submission of corroborating information in annual reports should occur as follows:

- Corroborating information specified in section III (Phase 2 Studies) that is generated during phase 1 need not be submitted until the first annual report after initiation of phase 2 studies. However, a sponsor can choose to submit the information in annual reports during phase 1 studies.

- Corroborating information specified in section III (Phase 2 Studies) that is generated during phase 2 studies should be submitted in the next annual report after the information becomes available. Corroborating information specified in section III need not be submitted before initiating phase 2 clinical trials.

- Corroborating information specified in section IV (Phase 3 Studies) that is generated earlier during phase 1 and phase 2 need not be submitted until the first annual report after initiation of phase 3 studies. However, a sponsor can choose to submit the information in annual reports during phase 1 and phase 2 studies.

[4] Although FDA's review of phase 1 submissions will focus on assessing the safety of phase 1 investigations, FDA's review of phases 2 and 3 submissions will include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for market approvals (21 CFR 312.22(a)).

- Corroborating information specified in section IV (Phase 3 Studies) that is generated during phase 3 studies should be submitted in the next annual report after the information becomes available. Corroborating information specified in section IV need not be submitted before initiating phase 3 clinical trials.

III. PHASE 2 STUDIES

The CMC information provided to support the phase 2 studies should focus on additional CMC information to maintain the continued safety of the patients enrolled in these studies. Corroborating information should be provided to ensure that the clinical investigations will yield reliable and interpretable data. During or before phase 2, CMC safety information that has previously been submitted to the IND may have changed and consequently must be updated as required under 21 CFR 312.31.[5] For information amendments submitted to the IND during ongoing development, the emphasis should be on reporting significant changes that can have a safety-related impact. These include, but are not limited to, those changes specified in section II.B.1. In cases where studies begin with phase 2 clinical studies, CMC safety information should be submitted before initiation of the phase 2 studies as specified in the phase 1 guidance and in this section.

The information recommended in sections III.A and III.B is considered CMC safety information that should be submitted in an information amendment before initiation of phase 2 studies, except where particular information is identified for submission in an annual report (i.e., corroborating information). Information that is considered corroborating information that can be submitted in an annual report is indicated in sections III.A.5, 6, and 7 and III.B.5 and 6.

Sponsors can reference an official compendium or other FDA recognized standard reference (e.g., *AOAC International Book of Methods*) to provide certain recommended CMC information (e.g., general methods, monograph standard) for an investigational drug substance or drug product, when applicable.[6] Reference to drug master files (DMFs) or other existing INDs or NDAs, with an authorization letter from the holder, sponsor, or applicant, can also be used to provide CMC information in support of the IND submission (21 CFR 312.23(b)).

A. Drug Substance

1. General Information

The Agency recommends that sponsors provide updates on the brief description of the drug substance, which was provided to support the phase 1 studies, and a more detailed description of the configuration and chemical structure for complex organic compounds (e.g., paclitaxel, polyketides). This information will be helpful in predicting the structure

[5] Throughout section III, the guidance indicates that updates of or changes in CMC safety information from that provided for phase 1 should be submitted. This statement refers to updates that are warranted because changes are being made for materials intended for phase 2 studies. If changes relate to materials used in phase 1 studies, the changes should have been reported during the phase 1 studies.

[6] Official compendium is defined in section 201(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(j)).

of possible metabolites. For peptides, characterization should include data on the amino acid sequence, and when relevant, peptide map. For DNA products, characterization should include nucleic acid sequence, DNA melting point, and side chain modifications when applicable.

2. Manufacture

a. Manufacturers

The addition, deletion, or change of any manufacturer of the drug substance from that specified during phase 1 should be reported.

b. Description of Manufacturing Process and Process Controls

An updated flow diagram for the synthesis or manufacturing process should be provided, if applicable. This information can be a general description. However, the flow diagram should contain the chemical structures and configurations, including stereochemical information of the starting materials, intermediates (either in situ or isolated), and, when feasible, significant side products. Reagents, solvents and auxiliary materials, equipment (e.g., fermenters, columns), and provisions for monitoring and controlling critical conditions should be identified. Furthermore, a manufacturing step should be described in more detail if it is unique or critical to the synthetic or manufacturing process. For example, for fermentation and natural source drug substances, identification of model number or manufacturer of the fermenter is not warranted, but process controls that ensure performance of safety-related manufacturing steps (e.g., viral or impurity clearance) should be clearly described.

The general description of the synthetic and manufacturing process (e.g., fermentation, purification) provided to support the phase 1 studies should be updated from a safety perspective if changes or modifications have been introduced**.** Reprocessing procedures and controls need not be described except for natural source drug substances when the steps affect safety (e.g., virus or impurity clearance).

For sterile drug substances, updates on the manufacturing process from that provided for phase 1 studies should be submitted. The phase 2 information should include changes in the drug substance sterilization process (e.g., terminal sterilization to aseptic processing). Information related to the validation of the sterilization process need not be submitted at this time.

c. Control of Materials

The structures of the proposed starting materials should be provided if they have not been previously submitted. The source, analytical procedures, and test results for the starting materials should be submitted upon request. A list of any new

reagents, solvents, auxiliary materials, or biological raw materials should be provided. For critical, complex materials (e.g., monoclonal antibodies configured in affinity matrices), a full description of the manufacturing process and acceptance criteria for the material should be provided.

For fermentation products or natural substances extracted from plant, human, or animal sources, the following information would have been provided in phase 1: (1) origin (e.g., country), source (e.g., pancreas), and taxonomy (e.g., family, genus, species, variety) of the starting materials or strain of the microorganism; (2) details of appropriate screening procedures for adventitious agents, if relevant; and (3) information to support the safe use of any materials of microbial, plant, human, or animal origin (e.g., certification, screening, testing). Any updates to the information submitted in phase 1 and any new information to support the safety of materials of human or animal origin should be provided.

d. Controls of Critical Steps and Intermediates

To the extent possible in phase 2, sponsors should provide information on controls of critical steps and intermediates and tentative acceptance criteria to ensure that the manufacturing process is controlled at predetermined points. Although controls of critical steps and intermediates can still be in development, information on controls for monitoring adventitious agents should be provided for fermentation and natural source (human or animal) drug substances, as appropriate.

3. Characterization

Evidence to reasonably support the proposed chemical structure of the drug substance should be provided. Data on particle size distribution and other physical properties (e.g., polymorphic or solid state form) should be generated so that relevant correlations can be established between data generated during early and late drug development. Data on the particle size distribution and/or physical properties should be submitted, when appropriate (e.g., inhalation, suspension, modified release solid dosage forms).

4. Control of Drug Substance

A *specification sheet* is a list of tests, analytical procedures, and acceptance criteria (i.e., numerical limits, ranges, or other criteria for the tests described). Critical quality attributes include, but are not limited to, identity, purity, quality, potency or strength, and impurities. During the clinical investigation process, the sponsor would establish tentative acceptance criteria that are continually refined based on data obtained from analysis of batches of drug substance and new information that becomes available. In the course of product development, the analytical technology or methodology often evolves parallel to the clinical investigations. In setting subsequent acceptance criteria, relevant correlations should be established between data generated during early and late drug development.

Any change in the tentative specification, including the tentative acceptance criteria, should be reported. This includes changes in the sponsor's drug substance specification and, if different, drug product manufacturer's acceptance testing for the drug substance. Test results and analytical data (e.g., infrared spectra, chromatograms) from batch release of representative clinical trial materials should be provided initially and when any change is made in the specification.

The analytical procedure (e.g., high-pressure liquid chromatography) used to perform a test and to support the tentative acceptance criteria should be briefly described and changes reported when the changes are such that an update of the brief description is warranted. A complete description of analytical procedures and appropriate validation data should be available for the analytical procedures that are not from an FDA-recognized standard reference (e.g., official compendium, *AOAC International Book of Methods*), and this information should be submitted upon request.

New impurities (e.g., from a change in synthetic pathway) should be qualified, quantified, and reported, as appropriate. Procedures to evaluate impurities to support an NDA (e.g., recommended identification levels) may not be practical at this point in drug development. Suitable limits should be established based on manufacturing experience, stability data, and safety considerations.

5. Reference Standards or Materials

Where a recognized national or international standard (such as a standard from the World Health Organization (WHO)) is available, the manufacturer's reference material and/or working standard should be qualified against this standard. A national or international reference standard may not be available because many INDs will be for new molecular entities. In this case, the sponsor can select a batch of drug substance to be used as a reference material, against which initial clinical batches would be tested before their release. Preferably, the sponsor would establish a working standard even at the initial stage of drug development. For the purpose of this guidance, a *working standard* is a reference material that has been further characterized beyond the standard batch release tests. The protocol for establishing the working standard should be submitted in an information amendment. However, the results from the testing to establish the working standard can be reported in an annual report.

When a reference material is fully characterized, it would become the manufacturer's primary reference material. The manufacturer can continue to establish new working standards that are qualified against that primary reference material.

6. Container Closure System

The *container closure system* is defined as the sum of packaging components that together contain and protect the drug substance. A brief description of the container closure system (also referred to as the packaging system) and any subsequent changes

should be provided in an annual report.

7. Stability

A description of the stability program to support the drug substance under clinical investigation in phase 2 should be submitted that includes a list of tests, analytical procedures, acceptance criteria, test time points for each of the tests, storage conditions, and the duration of the study.

Any available stability data for the clinical material used in the phase 1 study that were not reported during phase 1 should be provided in an information amendment. Stability data from representative clinical trial materials used in phase 2 should be provided in annual reports as the data become available.

If degradation of the drug substance occurs during manufacture or storage, this change should be considered when establishing acceptance criteria and monitoring quality. Because of the inherent complexity of many drug substances, there may be no single stability-indicating assay or parameter that profiles all the stability characteristics of the drug substance. Consequently, the manufacturer should consider the development of stability-indicating analytical procedures that will detect significant changes in the quality of the drug substance. The nature of the particular drug substance will determine which tests should be included in the stability program. Performance of stability stress studies with the drug substance early in drug development is encouraged, as these studies provide information crucial to the selection of stability indicating analytical procedures for real time studies.

B. Drug Product

1. Description and Composition of the Drug Product

Any changes from the information specified for phase 1 (i.e., table listing of all components) should be provided. All components used in the manufacture of the drug product, regardless of whether or not they appear in the finished drug product, should be identified by their established names and a reference to a quality standard (e.g., *United States Pharmacopeia* (USP), *National Formulary* (NF)) included. The quantitative composition on a per unit basis (e.g., milligram (mg)/milliliter (mL), mg/tablet) should be provided. However, quantitative values need not be reported for components that are removed during manufacturing and do not appear in the final drug product.

2. Manufacture

a. Manufacturers

The addition, deletion, or change of any manufacturer of the drug product from that specified during phase 1 should be reported**.**

b. Batch Formula

A representative batch formula should be provided if not already submitted. Quantitative information should be reported for all components in the batch formula whether or not the component appears in the final drug product.

c. Description of Manufacturing Process and Process Controls

An updated flow diagram and a brief step-by-step description of the manufacturing process should be provided**.** The description can focus on the unit operation (e.g., blending) rather than the individual manufacturing steps of the unit operation. Information, such as the following, need not be provided in either the flow diagram or description: (1) equipment used (e.g., V-blender); (2) the packaging and labeling process; (3) controls, except for sterile products (e.g., injectables, implants, ophthalmics) or atypical dosage forms (e.g., metered dose inhalation (MDI), liposomal encapsulation, implants, injectable microspheres); and (4) information on reprocessing procedures and controls, unless it is safety related. Where the qualitative formulation does not change, a single description of the manufacture of different strength unit doses can be provided.

For sterile products, updates on the manufacturing process from that provided for phase 1 studies should be submitted. The phase 2 information should include changes in the drug product sterilization process (e.g., terminal sterilization to aseptic processing). Information related to the validation of the sterilization process need not be submitted at this time.

3. Control of Excipients

For compendial excipients, references to quality standards (e.g., *USP*, *NF*) should be provided if changed from phase 1.

For noncompendial excipients, a specification sheet should be provided that identifies the tests and acceptance criteria and indicates the types of analytical procedure (e.g., HPLC) used. A complete description of the analytical procedures should be submitted upon request. A brief description of the manufacture and control of these components or an appropriate reference should be provided (e.g., DMF, NDA). Information for excipients not used in previously approved drug products in the United States (e.g., novel excipients) should be equivalent to that submitted for drug substances.

4. Control of Drug Product

Physicochemical tests (e.g., identity, assay, content uniformity, degradants, impurities, dissolution, viscosity, particle size), biological (e.g., potency), and microbiological tests (e.g., sterility and pyrogens or bacterial endotoxins for sterile products, antimicrobial preservative for multiple-dose sterile and nonsterile dosage forms, and microbial limits for nonsterile dosage forms) that have been added or deleted from the specification

should be reported. Data on the particle size distribution and/or polymorphic form of the drug substance used in clinical trial materials should be included, when appropriate (e.g., inhalation, suspension, modified release solid dosage forms) so that relevant correlations can be established between data generated during early and late drug development and in vivo product performance. Relaxation of acceptance criteria or any change that affects safety should be reported. Test results and analytical data (e.g., chromatograms) from batch release of representative clinical trial materials should be provided initially and when any changes are made in the specification.

The analytical procedure (e.g., HPLC) used to perform a test should be briefly described and changes reported when the change is such that an update of the brief description is warranted. A complete description of analytical procedures and appropriate validation data should be available for analytical procedures that are not from an FDA-recognized standard reference (e.g., official compendium, *AOAC International Book of Methods*), and this information should be submitted upon request.

Data updates on the degradation profile should be provided so safety assessments can be made.

5. Container Closure System

The *container closure system* is defined as the sum of packaging components that together contain and protect the drug product. A brief description of the container closure system (also referred to as *packaging system*) should be provided in an information amendment. When changes are made in the container closure system, information should be submitted in an information amendment if there can be an effect on product quality. Otherwise, the changes can be reported in an annual report. Additional information may be requested for atypical delivery systems (e.g., MDIs, disposable injection devices).

6. Stability

A description of the stability program to support phase 2 clinical studies should be submitted that includes a list of the tests, analytical procedures, acceptance criteria, test time points for each of the tests, storage conditions, and the duration of the study, which should be long enough to cover the expected duration of the clinical studies.

Any stability data for the clinical material used in the phase 1 study that were not reported during phase 1 should be provided in an information amendment. The stability of reconstituted products should be studied and data submitted if not already provided or when there are formulation or diluent changes. Stability data from representative clinical trial materials used in phase 2 should be provided in annual reports as the data become available.

If degradation of the drug product occurs during manufacture or storage, this change should be considered when establishing acceptance criteria and monitoring quality.

Because of the inherent complexity of many dosage forms, there may be no single stability-indicating assay or parameter that profiles all the stability characteristics of the drug product. Consequently, the manufacturer should consider the development of stability-indicating analytical procedures that will detect significant changes in the quality of the drug product. The nature of the particular drug product will determine which tests should be included in the stability program.

IV. PHASE 3 STUDIES

CMC development continues in parallel with the clinical development during phase 3 studies. The CMC safety information provided to support phase 3 studies should focus on the information that is warranted in maintaining the continued safety of the patients enrolled in these studies. For information amendments submitted to the IND during ongoing development, the emphasis should be on reporting significant changes that can have a safety-related impact. During or before phase 3, CMC safety information that has previously been submitted to the IND may have changed and, consequently, should be updated as required under § 312.31.[7] These changes include, but are not limited to, those specified in section II.B.1. The corroborating information should be provided in the annual report to ensure that the clinical investigations will yield reliable and interpretable data.

Sponsors can reference an official compendium or other FDA-recognized standard reference (e.g., *AOAC International Book of Methods*) to provide certain recommended CMC information (e.g., general methods, monograph standard) for an investigational drug substance or drug product, when applicable. Reference to DMFs or other existing INDs or NDAs, with an authorization letter from the holder, sponsor or applicant, can also be used to provide CMC information in support of the IND submission (21 CFR 312.23(b)).

Before the phase 3 studies, the sponsor can have an *end-of-phase-2* meeting, or during the phase 3 studies, a CMC specific *end-of-phase-2* meeting, with the Agency. As part of the preparation for that meeting, a background document is often provided that can be a valuable information amendment to the IND. The document would include updates to describe the materials already used and/or to be used in phase 3 studies, as well as put the studies performed to date in context with the prospective strategy for the ultimate NDA.

A. Drug Substance

1. General Information

General descriptive information on the physical, chemical, and biological characteristics of the drug substance should be provided in an annual report. This information, if not

[7] Throughout section IV, the guidance indicates that updates of or changes in CMC safety information from that provided for phase 1 or phase 2 should be submitted. This statement refers to updates that would be warranted because changes are being made for materials intended for phase 3 studies. If changes relate to materials used during phase 1 or phase 2 studies, the changes should have been reported, as warranted, during those studies.

previously submitted, can include (1) neutralization equivalents; (2) solubility properties, partition coefficient, dissociation constant (pKa), and isoelectric point (pI); (3) hygroscopicity; (4) crystal properties and morphology determined by thermal analysis (e.g., DSC, TGA),[8] powder X-ray diffraction and microscopy; (5) particle size and surface area; (6) melting point and boiling point; (7) optical rotation; (8) stereochemistry; and (9) biological activities, if applicable.

2. Manufacturer

a. Manufacturers

A list of all firms associated with the manufacture of the drug substance should be provided in an information amendment, including contract facilities used for manufacturing and/or testing (e.g., stability studies, quality control release testing).

b. Description of Manufacturing Process and Process Controls

An updated flow diagram should be provided in an information amendment when changes occur. A general step-by-step description of the synthesis and manufacturing processes, including the final isolation of the drug substance, should be provided in an annual report. Examples of relevant information that should be included in the description are as follows: (1) batch size (range); (2) relative ratios of reagents, solvents, and auxiliary materials; (3) process controls (brief description of the analytical procedures) and general operating conditions (time, temperature); (4) controls of critical steps and intermediates; (5) control of crystalline forms; and (6) literature references for any novel reactions or complex mechanisms. Reprocessing procedures and pertinent controls should be described in an annual report, except when reprocessing steps for fermentation or natural source drug substances are likely to affect safety (e.g., virus or impurity clearance). In this case, new or updates of previously submitted reprocessing information should be provided in an information amendment.

For sterile drug substances, updates on information from that provided in phase 1 and phase 2 should be submitted in an information amendment. The information should include a description of changes in the drug substance sterilization process (e.g., terminal sterilization to aseptic processing). Information related to the validation of the sterilization process need not be submitted at this time but should be submitted at the time of an NDA filing (see FDA guidance *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*).

c. Control of Materials

[8] Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

In addition to the information provided during phase 1 and phase 2, analytical procedures and acceptance criteria for assessing the quality of starting materials should be provided in an information amendment. Furthermore, a list of any new reagents, solvents, auxiliary materials, or biological raw materials should be provided in an information amendment. For critical, complex materials (e.g., monoclonal antibodies configured in affinity matrices), changes to the description of the manufacturing process and acceptance criteria should also be provided in an information amendment.

In an annual report, a table listing all reagents, solvents, and catalysts should be submitted that includes (1) a reference to a quality standard for each material used and (2) the specific identity test performed upon receipt of the material. When warranted, a more comprehensive list of tests and acceptance criteria should be submitted in an annual report for special reagents (e.g., reagents for kinetic resolution, sera, enzymes, or proteins).

Information should be provided in an information amendment to (1) update the information submitted in phase 1 and phase 2 regarding the origin of fermentation products or natural substances extracted from plant, human, or animal sources and (2) provide any new information to support the safety of materials of human or animal origin.

d. Controls of Critical Steps and Intermediates

Controls at critical steps in the synthesis or manufacturing process that ensure reaction completion, identity, purity or proper cell growth, and changes in critical controls reported during phase 2, should be described in an information amendment. For fermentation and natural source drug substances, changes to process controls that ensure performance of safety-related manufacturing steps (e.g., viral or impurity clearance) should be clearly described. Changes in controls for monitoring adventitious agents should be provided for fermentation and natural source drug substances, as appropriate.

For isolated intermediates that are controlled, the analytical procedures and tentative acceptance criteria should be described in an annual report. Tentative acceptance criteria can be used to allow for flexibility in the development process but should fulfill the primary purpose of quality control. The description of the analytical procedures can be brief, and appropriate validation information should be submitted upon request.

3. Characterization

Updates on the information previously provided during phase 2 should be provided in information amendments. The information amendment should include evidence to support the elucidation and characterization of the structure, which augments the information provided in phase 2. This information can include elemental analysis,

conformational analysis, molecular weight determination, spectra from IR, NMR (^{1}H & ^{13}C), UV, MS, optical activity, and if available, single crystal X-ray diffraction data, if not previously provided.[9]

Analytical procedures used to characterize the primary reference material should also be provided in an information amendment. (See section IV.A.5)

4. Control of Drug Substance

A detailed listing of all the tests performed on the drug substance (e.g., description, identity, assay, impurities, residual solvents) and the tentative acceptance criteria should be provided in an information amendment. A list should be provided for the testing performed by the sponsor and, if different, the drug product manufacturer. Test results and analytical data (e.g., infrared spectra, chromatograms) from batch release of representative clinical trial materials should also be provided in an information amendment initially and when any changes are made in the specification.

Information on the analytical procedures should be provided in an annual report. A general description of the analytical procedures should be provided that includes a citation to an official compendium, other FDA-recognized standard reference, or the sponsor's standard test procedure number, as appropriate. A description of analytical procedures with appropriate validation information should be provided for the analytical procedures that are not from an FDA-recognized standard reference (e.g., official compendium, *AOAC International Book of Methods*).

New impurities (e.g., from a change in synthetic pathway) should be identified, qualified, quantified, and reported**,** as appropriate. Procedures to evaluate impurities to support an NDA (e.g., recommended identification levels) may not be practical at this point in drug development. Suitable limits should be established based on manufacturing experience, available stability data, and safety considerations.

Suitable microbial limits should be established for nonsterile products that have potential to support microbial growth, if not previously submitted. These limits or changes in previously reported limits should be reported in an information amendment.

5. Reference Standards or Materials

If a national or international standard is not yet available, the sponsor should establish its own primary reference material during phase 3 studies. The manufacturer can continue to use the working standard from phase 2 or can establish a new working standard for lot release. The synthesis and purification of the primary reference material and/or working standard should be described in an information amendment if it differs from that of the investigational drug substance. The analytical procedures for and results from qualifying

[9] Infrared spectrometry (IR), nuclear magnetic resonance spectrometry (NMR), ultraviolet spectrometry (UV), and mass spectrometry (MS).

the working standard against the primary reference material should be provided in an annual report.

Where a recognized national or international standard is available and appropriate, the manufacturer's reference material and/or working standard should be qualified against this standard, and the results provided in an annual report.

6. Container Closure System

Any changes in the container closure system used to transport and/or store the bulk drug substance should be described in an annual report.

7. Stability

Changes in the drug substance stability program from that described for phase 2 (see section III.A.7) should be provided in an information amendment. Furthermore, the stability program should be updated to include descriptions of the stress and accelerated studies, if not previously described in phase 2. A container closure system that simulates the container closure system used to transport and/or store the bulk material can be used for the drug substance stability studies. Tests unique to the drug substance stability program (i.e., tests not included in section IV.A.4) should be defined and described.

Any stability data for the clinical material used in the phase 2 studies that were not reported during phase 2 should be provided in an information amendment. Stability data for representative clinical trial materials used in phase 3 should be provided in annual reports in tabular format as the data become available. The submitted stability information should include the lot number, manufacturer, manufacturing site, and the date of manufacture of the drug substance.

If not performed earlier, stress studies should be conducted during phase 3 to demonstrate the inherent stability of the drug substance, potential degradation pathways, and the capability and suitability of the proposed analytical procedures. The stress studies should assess the stability of the drug substance in different pH solutions, in the presence of oxygen and light, and at elevated temperatures and humidity levels. These one-time stress studies on a single batch are not considered part of the formal stability program. The results should be summarized and submitted in an annual report.

To ensure appropriate stability data are generated for filing at the NDA stage, a stability protocol that will be used for the formal stability studies should be developed.[10] The analytical procedures should be referenced to the drug substance specification section of the IND or an official compendium, if possible. Tests unique to the stability protocol should be defined and described. It is helpful if the stability protocol is submitted in an

[10] Applicants should refer to the forthcoming guidance *Stability Testing of Drug Substances and Drug Products,* when finalized, for information on stability protocols for formal stability studies. In June 1998 (63 FR 31224), the Agency made available a draft version of this guidance.

information amendment before or during phase 3 studies and is discussed at the end-of-phase-2 meeting.

B. Drug Product

1. Description and Composition of the Drug Product

The sponsor should provide updated information regarding the components and composition in an information amendment if different from that reported in phase 1 and/or phase 2. The formulation for certain drug products delivered by devices (e.g., MDIs, dry powder inhalation (DPIs), and nasal sprays) should be similar to that intended for the marketed drug product.

2. Manufacture

a. Manufacturers

A listing of all firms associated with the manufacture of the drug product should be provided in an information amendment, including any contract facilities used for manufacturing and/or testing (e.g., stability studies, packaging, labeling, quality control release testing).

b. Batch Formula

The sponsor should provide updated representative batch formula in an information amendment if different from that used in phase 1 and/or phase 2.

c. Description of Manufacturing Process and Process Controls

Changes in the manufacturing method for the drug product should be provided. An updated flow diagram and description of the manufacturing process (excluding packaging and labeling) should be provided in an information amendment. The description should indicate how the material is being processed and can be general enough to allow for flexibility in development. Reprocessing procedures and pertinent controls should be described in an information amendment, if applicable. A brief description of the packaging and labeling process for clinical supplies should be provided in an annual report.

For sterile products, updates on information from that provided for phase 1 and phase 2 should be submitted in an information amendment. The information should include a description of changes in the drug product sterilization process (e.g., terminal sterilization to aseptic processing). Information related to the validation of the sterilization process need not be submitted at this time but should be submitted at the time of an NDA filing (see FDA guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*).

3. Control of Excipients

Updates on compendial excipient information previously provided should be submitted in information amendments. In certain cases, testing in addition to that specified in a compendium (e.g., functionality) can be useful and should be proposed.

For a noncompendial excipient, updates and a full description of the characterization, manufacture, control, analytical procedures, and acceptance criteria should be provided in an information amendment. Alternatively, a reference with authorization to a DMF can be provided. Information for excipients not used in previously approved drug products in the United States (e.g., novel excipients) should be equivalent to that submitted for new drug substances.

4. Control of Drug Product

A detailed listing of all the tests performed on the drug product and the tentative acceptance criteria should be provided in an information amendment. A summary table of test results and analytical data (e.g., chromatograms) from batch release of representative clinical trial materials should be provided in an information amendment initially and when any changes are made in the specification. Data on the particle size distribution and/or polymorphic form of the drug substance used in clinical trial materials should be included, when appropriate (e.g., inhalation, suspension, modified release solid dosage forms), so that relevant correlations can be established between data generated during early and late drug development and in vivo product performance.

A general description of the analytical procedures used should be provided in an annual report that includes a citation to an official compendium, other FDA-recognized standard reference, or the sponsor's standard test procedure number, as appropriate. A description of the analytical procedure with appropriate validation information should be provided for analytical procedures that are not from an FDA-recognized standard reference (e.g., official compendium, *AOAC International Book of Methods*).

Data updates on the degradation profile should be provided in an information amendment so safety assessments can be made. Degradation products should be identified, qualified, quantified, and reported**,** as appropriate. Evaluation procedures to support an NDA's degradants (e.g., recommended identification levels) may not be practical at this point in drug development. Suitable limits should be established based on manufacturing experience, stability data, and safety considerations.

For sterile-preserved products in multiple-dose containers or nonsterile-preserved products, a citation to the USP Antimicrobial Preservative-Effectiveness Test (APET) or a description of an equivalent procedure with the associated test validation information should be provided in an information amendment. This test should be performed at the lowest specified concentration of antimicrobial preservative specified for the drug product at release or at the end of the expiration dating period, whichever is less. The

efficacy of preservative systems is evaluated based on their effect on inoculated microorganisms.

A dissolution testing program for oral immediate release dosage forms (e.g., tablets, capsules, suspensions) and a drug release program for modified release dosage forms (e.g., modified release tablets, capsules, suspensions, transdermal drug delivery systems) should be developed. Dissolution or drug release characteristics of a drug product, particularly the selection of the medium, are generally based on the pH solubility profile and pKa of the drug substance. Dissolution or drug release profiling should be performed in physiologically relevant media with reasonable speeds of rotation (e.g., basket at 50 or 100 rotations per minute (rpm), paddle at 50 rpm). The dissolution or drug release program at phase 3 should bring commonality to both the methodology and the proposed acceptance criteria by taking into consideration the results of dissolution or drug release testing of clinical, bioavailability, and bioequivalence batches (e.g., clinically studied formulations versus the *to-be-marketed* formulation) and relevant stability batches. The overall aim is to set in vitro dissolution or drug release acceptance criteria that ensure batch-to-batch and unit-to-unit consistency, post-NDA approval. The sponsor is encouraged to obtain concurrence on choice of apparatus, medium, rotation speed, and sampling time points from the Agency before the primary stability studies are initiated. Discussions with the Agency (e.g., at the end-of phase-2 meeting) can also include plans for establishing an in vivo-in vitro correlation (IVIVC) and characterizing the drug substance using the Biopharmaceutics Classification System (BCS).

5. Container Closure System

An update of the description of the container closure system should be provided in an information amendment if it differs from that reported during phase 2. When changes are made in the container closure system during phase 3 studies, information should be submitted in an information amendment if there can be an effect on product quality. Otherwise, the changes can be reported in an annual report.

For packaging components with compendial standards (e.g., glass, polyethylene containers), compliance with the appropriate compendial standards should be stated. If the sponsor refers to information in a Type III DMF, an authorization letter from the DMF holder should be provided. Additional information may be requested for atypical delivery systems (e.g., MDIs, disposable injection devices). The container closure system of certain drug products delivered by devices (e.g., MDIs, DPIs, nasal sprays) should be similar to that intended for the marketed drug product. A sponsor can consult with the appropriate CMC review team for additional guidance if it has any questions.

6. Stability

A stability program should be designed to monitor the chemical, physical, biological, or microbiological (if applicable) stability of the drug product throughout the clinical testing program. Changes in the drug product stability program from that described for phase 2 (see section III.B.7) should be provided in an information amendment. A brief

description should be provided in an information amendment for each of the attributes being investigated in the stability program (i.e., long-term and accelerated), demonstrating that the appropriate controls and storage conditions are in place to ensure the quality of the product used in clinical trials. Furthermore, tests unique to the drug product stability program (i.e., tests not included in section IV.B.4) should be adequately defined and described.

Any stability data for the clinical material used in the phase 2 studies that were not reported during phase 2 should be provided in an information amendment. Stability data for representative clinical material used in phase 3 should be provided in annual reports in tabular format as the data become available. The submitted information should include the batch number, manufacturing site, date of manufacture of the drug product, and relevant information on the drug substance (e.g., lot number, manufacturer) used to manufacture the drug product. The analytical results for each test should be reported. Representative chromatograms should be provided in the annual report, if applicable.

For certain drug products, one-time stress testing can be warranted to assess the potential for changes in the physical (e.g., phase separation, precipitation, aggregation, changes in particular size distribution) and/or chemical (e.g., degradation and/or interaction of components) characteristics of the drug product. The studies could include testing to assess the effect of high temperature, humidity, oxidation, photolysis and/or thermal cycling. The relevant data should be provided in an annual report.

To ensure appropriate stability data are generated for filing at the NDA stage, a stability protocol that will be used for the formal stability studies should be developed.[11] The analytical procedures should be referenced to the control of drug product section of the IND or an official compendium, if possible. Tests unique to the stability protocol should be defined and described. It is helpful if the stability protocol is submitted in an information amendment before or during phase 3 studies and is discussed at the end-of-phase-2 meeting, especially for those protocols including bracketing and matrixing approaches.

V. PLACEBO

A brief, general description of the composition, manufacture, and control of the placebo provided during phase 1 should be updated or provided for phase 2 and/or phase 3 if the placebo is being used for the first time. This information and any updates to this information should be provided in an information amendment. When placebos are used in clinical trials, the placebo clinical study materials should be tested to demonstrate the absence of the drug substance**.** The results from the placebo testing should be submitted in an annual report.

[11] Applicants should refer to the forthcoming guidance *Stability Testing of Drug Substances and Drug Products,* when finalized, for information on stability protocols for formal stability studies. In June 1998 (63 FR 31224), the Agency made available a draft version of this guidance.

VI. LABELING

Updates of the information provided for phase 1 should be submitted in information amendments during phase 2 and phase 3.

VII. ENVIRONMENTAL ASSESSMENTS

Updates on information already submitted and on whether a claim for a previous categorical exclusion has changed should be provided in information amendments for phase 2 and phase 3 (see FDA guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications*).

RESOURCES

FDA continues to update existing and publish new guidance documents. An applicant should ensure that it is using current guidance when preparing a submission. CDER guidances are available on the Internet at http://www.fda.gov/cder/guidance/index.htm**.**

ICH Guidances

Although not intended to be applicable to IND applications, the International Conference on Harmonization (ICH) documents below can serve as valuable resources in guiding the course of product development.

ICH *Q1A Stability Testing of New Drug Substances and Products*

ICH *Q1B Photostability Testing of New Substances and Products*

ICH *Q1C Stability Testing for New Dosage Forms*

ICH *Q2A Validation of Analytical Procedures*

ICH *Q2B Validation of Analytical Procedures: Methodology*

ICH *Q3A Impurities in New Drug Substances*

ICH *Q3B Impurities in New Drug Products*

ICH *Q3C Impurities: Residual Solvents*

ICH *Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin*

ICH *Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products*

ICH *Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products*

ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

ICH *Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*

FDA Guidances for Industry

Draft FDA guidances are cited for completeness of information and are not for implementation until finalized.

Analytical Procedures and Methods Validation — Chemistry, Manufacturing, and Controls Documentation, Draft. The Agency published this draft guidance in the *Federal Register* on August 30, 2000 (65 FR 52776).

Botanical Drug Products, Draft. The Agency published this draft guidance in the *Federal Register* on August 11, 2000 (65 FR 49247).

Container Closure Systems for Packaging Human Drugs and Biologics

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

Drug Product: Chemistry, Manufacturing, and Controls Information, Draft. The Agency published this draft guidance in the *Federal Register* on January 28, 2003 (68 FR 4219).

Drug Substance: Chemistry, Manufacturing, and Controls Information (forthcoming guidance)

Environmental Assessment of Human Drug and Biologics Applications

Fast Track Drug Development Programs – Designation, Development, and Applications Review

IND Meetings for Human Drugs and Biologics — Chemistry, Manufacturing, and Controls Information

Monoclonal Antibody Used as Reagents in Drug Manufacturing

Stability Testing of Drug Substances and Drug Products, Draft. The Agency published this draft guidance in the *Federal Register* on June 8, 1998 (63 FR 31224).

Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances

Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products